Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up

Katja Pietz, Peter Hagell, Per Odin

Abstract

***Objectives*—Despite the recent introduction of new peroral drugs as well as neurosurgical methods for Parkinson's disease, treatment of late stage parkinsonian patients remains difficult and many patients become severely handicapped because of fluctuations in their motor status. Injections and infusions of apomorphine has been suggested as an alternative in the treatment of these patients, but the number of studies describing the effects of such a treatment over longer time periods is still limited. The objective was to investigate the therapeutic response and range of side effects during long term treatment with apomorphine in advanced Parkinson's disease.**

***Methods*—Forty nine patients (30 men, 19 women; age range 42–80 years) with Parkinson's disease were treated for 3 to 66 months with intermittent subcutaneous injections or continuous infusions of apomorphine.**

***Results*—Most of the patients experienced a long term symptomatic improvement. The time spent in "off" was significantly reduced from 50 to 29.5% with injections and from 50 to 25% with infusions of apomorphine. The quality of the remaining "off" periods was improved with infusion treatment, but was relatively unaffected by apomorphine injections. The overall frequency and intensity of dyskinesias did not change. The therapeutic effects of apomorphine were stable over time. The most common side effect was local inflammation at the subcutaneous infusion site, whereas the most severe were psychiatric side effects occurring in 44% of the infusion and 12% of the injection treated patients.**

***Conclusion*—Subcutaneous apomorphine is a highly effective treatment which can substantially improve the symptomatology in patients with advanced stage Parkinson's disease over a prolonged period of time.**

(*J Neurol Neurosurg Psychiatry* 1998;**65**:709–716)

Keywords: Parkinson's disease; apomorphine; dopamine agonist; treatment

Section of Restorative Neurology, Department of Clinical Neuroscience, Division of Neurology, University Hospital, S-221 85 Lund, Sweden
P Hagell
K Pietz
P Odin

Department of Neurology, Medical School Hannover, D-30623 Hannover, Germany
K Pietz
P Odin

Correspondence to:
Dr Katja Pietz, Department of Neurology, Medical School, Hannover, D-30623 Hannover, Germany.
Telephone 0049 511 532 3580; fax 0049 511 532 3115.

Received 25 February 1997
and in final form
6 May 1998
Accepted 15 June 1998

The management of patients with Parkinson's disease is often complicated by drug resistant fluctuations in motor performance appearing after some initial years of successful peroral treatment with levodopa alone or in combination with dopamine agonists and/or selegiline.[1] Lately, new levodopa preparations, as well as new adjunct drugs and neurosurgical methods have improved the treatment possibilities. However, many patients do still have incapacitating motor fluctuations and drug resistant "off" periods.To counteract such fluctuations in motor response, the need for a drug with a fast and reliable onset of effect is obvious. Further, there are indications that continuous dopaminergic stimulation may be favourable compared with the pulsatile action of regular oral drug treatment to avoid and ameliorate motor complications in Parkinson's disease.[2] Drugs and drug delivery systems giving more stable plasma and brain tissue concentrations are thus also of great interest.

Apomorphine, which originally was produced by acid treatment of morphine in the 19th century, has, due to its multiple effects (for example, emetic, expectorative, sedative, aphrodisiac), been widely applied in clinical medicine. In 1951, Schwab *et al* were the first to show a clinical antiparkinsonian effect of apomorphine.[3] Since then its pharmacological and antiparkinsonian properties have been studied extensively. Apomorphine exerts its antiparkinsonian effect by direct stimulation of striatal presynaptic and postsynaptic dopamine D1 and D2 receptors.[4] One prominent property of apomorphine, when using the subcutaneous route of administration, is a rapid onset of action (5–15 minutes) and a brief dose dependent duration of effect (<90 minutes).[5–9]

Despite its potent antiparkinsonian effects, the clinical use of apomorphine for the treatment of Parkinson's disease was limited until the 1980s due to its peripheral dopaminergic side effects such as nausea, vomiting, postural hypotension, and sedation. Most of these side effects can be controlled by oral administration of the peripheral dopamine antagonist domperidone (10–20 mg three times a day).[10] As most patients develop tolerance to these side effects, adjuvant domperidone is usually only necessary during the initial phase of treatment. Apomorphine has been used in the treatment of Parkinson's disease for more than a decade now, with reported valuable and long term effects in late stage Parkinson's disease.[11–35] Other routes, including nasal, sublingual, and rectal administration, have also been studied.[36–44] However, the subcutaneous route is still the most common and best tolerated way to administer the drug. Despite an increased use of apomorphine for the treatment of Parkinson's disease during the past years, the number of published studies investigating the effects of long term treatment in larger groups of patients is still limited.

The aim of this study was to further investigate the therapeutic effectiveness, dose requirements, and side effects of subcutaneous apomorphine injections and continuous infusions during long term treatment of parkinsonian patients.

Patients and methods

PATIENTS

Sixty patients (36 men, 24 women) with idiopathic Parkinson's disease were enrolled into the treatment programme. After a test period of 2 months from the initiation of apomorphine it was decided whether the patient should continue the treatment or not. Eleven of the 60 patients stopped the treatment during this test period and are not included in the main results section below. Of the 11 patients who dropped out, three did so because of psychiatric side effects, three because of insufficient effect, two because of technical difficulties handling the equipment, one because of haemolytic anaemia, one because of entering another study, and one because of death from an unrelated reason. The evaluation of most of the remaining 49 patients was carried out at two different time points. The group of patients who received apomorphine infusions were evaluated after a mean of 20.2 and 54.0 months, and the patients treated with apomorphine injections after a mean of 10.2 and 42.2 months. Patients who stopped the treatment during the study were also evaluated before doing so. All results refer to the latest evaluation except when otherwise stated.

Exclusion criteria for entering the study were cardiovascular, renal, haematological, or psychiatric diseases. Inclusion criteria were daily disabling "wearing off", "on-off" motor fluctuations, or diphasic dyskinesias despite optimised peroral antiparkinsonian treatment. The choice of treatment (intermittent subcutaneous injection or continuous subcutaneous infusion) was based on the patient's clinical condition, ability to handle the drug delivery device, and his or her personal wishes. The patients were thus not randomly allocated to the treatment groups.

RECRUITMENT OF THE PATIENTS AND DESIGN OF THE STUDY

Patient selection was based on assessments during a 5 day pretreatment assessment period at the movement disorder inpatient unit in the department of neurology, Lund university hospital, Sweden. This assessment period comprised optimisation of the peroral medication, measurements of orthostatic blood pressure and pulse, laboratory analyses (haematology, biochemistry, renal and liver functions, and urine analyses), ECG, continuous registration of motor fluctuations, an apomorphine test (described below), and a single dose levodopa test.[45] Only patients fulfilling the criteria for idiopathic Parkinson's disease, including positive levodopa and apomorphine responses were enrolled.[45]

About 1 month later the selected patients were readmitted for 2–5 weeks for initiation of apomorphine treatment. Their parkinsonian status on peroral antiparkinsonian treatment was recorded during a screening phase of 3 days before starting apomorphine. During the subsequent apomorphine dose finding period (3–14 days) the optimal apomorphine injection doses or infusion rates and bolus doses were individually titrated. Another 1–2 weeks were needed for optimisation of the doses and patient education. Follow up visits were organised every third month. Apomorphine and other antiparkinsonian treatments were individually optimised at each revisit.

All adverse effects were recorded. Orthostatic blood pressure and pulse were followed at each follow up visit, and laboratory analyses were repeated at least every 12 months.

Cognitive and psychiatric conditions were not assessed by any formal rating scales, but were included as a standard part of the clinical routine examination and observation during admission on follow up visits.

DRUG AND ADMINISTRATION

Intermittent injections of apomorphine (5 mg/ml; pH 3–4; Apoteksbolaget, Sweden) were given with injection pens (Insuject-X; Novo Nordisk A/S, Denmark; D-Pen 50 µl/click; Orion Diagnostica AB, Sweden). For the infusions we used the Pharmacia Deltec CADD-PCA 5800 portable infusion pumps connected to a 0.6 mm lumen baby intravenous cannula with PTFE catheter (Neoflon ®; Boc Ohmeda AB, Sweden). The lower abdominal area or anterolateral femoral region were favoured for subcutaneous application, but areas above the hips and at the outer aspects of the upper arms were also used. Infusion sets were changed at least once, often twice, a day.

APOMORPHINE TEST

An apomorphine test was performed on all patients to determine responsiveness, latency from injection to onset of effect, and duration of effect as well as side effects.[46 47] Apomorphine injections were given with an interval of at least 90 minutes. With stepwise increased doses, starting with 0.5–1.0 mg and increased by 0.5–1 mg/dose (maximal dose 6 mg) until either an antiparkinsonian effect, or unacceptable side effects appeared. The patients' global physical, motor, and mental conditions were continuously observed and recorded. Pulse and blood pressure (supine after 3 minutes and standing after 1 minute) were recorded at baseline and 10 minutes after each injection. The following variables were tested immediately before and every 15 minutes after each injection: (*a*) rigidity in wrists, elbows, neck, and knees; (*b*) tremor in head, and upper and lower limbs; (*c*) time to perform 20 pronation-supinations of the hand, and (*d*) time to walk 2×7 metres.

DOMPERIDONE

Twelve to twenty four hours before apomorphine administration the patient was given domperidone (10–20 mg, three times a day). After initiation of apomorphine treatment the domperidone dose could in most cases gradually

be reduced (by 10 mg/day) over the first 2 weeks and finally stopped.

INTERMITTENT INJECTION OF APOMORPHINE

When starting injection treatment, the antiparkinsonian drugs were left unchanged and 50% of the threshold dose found in the apomorphine test was given. This dose was increased in a stepwise manner by no more than 1.0 mg/day until an optimal effect was reached. The patient was instructed to inject apomorphine at the beginning of each "off" period and to repeat the dose after 15 minutes if there was no effect. The largest single dose allowed was 6 mg.

CONTINUOUS INFUSION OF APOMORPHINE

The levodopa doses were reduced by at least 30%, in most cases about 50%, before the apomorphine infusions (given as continuous 24 hour infusions) were started. Other dopamine agonists and anticholinergic drugs were stopped, whereas selegiline was left unchanged. The initial dose was 1 mg/h, which subsequently was increased in a stepwise manner by no more than 1 mg/h/day until an optimal effect or side effects occurred. When the patient's condition had been stable at a slightly suboptimal level for 2 days, extra bolus doses were added. These were titrated in the same way as the intermittent injection doses (see above).

EFFECT ON OFF PERIODS

The patients motor status ("off", "on", "on with dyskinesias") was recorded by a specialised nurse every 30 minutes during the awake part of the day for at least 2 days immediately before the start of treatment, during the entire dose finding and education period, and for 4–8 hours at every evaluation visit. The patients also kept daily "on-off" diaries for at least 1 week before each follow up visit.

EFFECT ON PARKINSONIAN SYMPTOMS

Assessments using the Hoehn and Yahr, Schwab and England, and the Obeso dyskinesia scale[45] were performed before treatment and at each follow up visit. In addition, the global impression of the treatment compared with the baseline condition was estimated independently by the patient and the examiner according to the following scale: clear improvement, slight improvement, no change, slightly worse condition, and much worse condition.

STATISTICS

Statistical evaluations were performed with the package SPSS. As descriptive statistics the median, minimum, and maximum of all values except age are presented in the tables. For age, the mean value (SD) was tabulated. The difference in mean age between groups was assessed by *t* test. The Wilcoxon test was used to compare values at different time points, the Mann-Whitney *U* test to compare groups. A univariate analysis of covariance (ANCOVA) was performed to investigate the possibility of confounding for patient age, duration of disease, duration of levodopa treatment, duration of "on-off" fluctuations, and the effect of the apomorphine treatment on the part of day in "off". Level of significance was set to α=0.05.

Table 1 Characteristics of 49 patients who received apomorphine therapy for >2 months

	Continuous infusion (n=25)	*Intermittent injection (n=24)*
Age (y)	64.7 (6.8)	58.9 (9.7)
Duration of disease (y)*	16.0 (6–27)	11.5 (3–25)
Duration of levodopa therapy (y)*	14.0 (5–23)	10.0 (3–23)
Duration of "on-off" fluctuations (y)*	9.0 (2–19)	4.0 (1–18)
Duration of apomorphine therapy (months)	44.0 (3–67)	22.0 (6–54)

Except for "age" (where mean (SD) are shown) data represent median (range).
*At inclusion in study.

Results

Twenty five patients were treated with continuous subcutaneous apomorphine infusion therapy supplemented by apomorphine boluses and 24 patients received intermittent subcutaneous apomorphine injections. Due to disease progression, four patients changed from injection to infusion therapy. The data from these four patients were included in the infusion treatment group. No patient changed from infusion therapy to injection.

CONTINUOUS APOMORPHINE INFUSION

Patient group

Twenty five patients (14 men, 11 women) received continuous apomorphine infusions for more than 2 months (median 44.0 months). Further patient characteristics are given in table 1. Five patients stopped the treatment: three because of psychiatric side effects and two because of insufficient effect.

Apomorphine and levodopa doses

The lowest effective dose in the apomorphine dose test before the start of treatment was 2.0 (range 0.75–4.0) mg, the latency to onset of effect 10.0 (5–30) minutes, and the duration of effect 45.0 (25–85) minutes. At the latest evaluation the infusion rate was 4.0 mg/h, the bolus dose size 1.6 mg, and the total daily dose 112.5 mg (table 2). The levodopa treatment could be reduced in 24 of the 25 patients. The daily levodopa dose before starting apomorphine treatment was significantly higher (900 mg/day) than at the final evaluation (450 mg/day) ($p=0.003$). Of the 24 patients reducing levodopa, eight patients were able to stop taking levodopa completely. The 16 patients who did not stop levodopa completely still significantly reduced ($p<0.001$) their total daily levodopa intake from 900 (550–2600) mg distributed over eight (4–20) doses a day at inclusion to 450 (112–1900) mg distributed over eight (3–15) doses a day at the final evaluation. After the first 1–2 months of dose titration, the levodopa and apomorphine doses underwent no further significant changes. The total daily levodopa dose was 400 (0–1150) mg after 1–2 months and 400 (0–1900) mg after a mean of 40.3 months of treatment. The total daily apomorphine dose was 93.0 (60–190) mg after 1–2 months and 116 (57–174) mg after a mean of 40.3 months. Three patients maintained the domperidone treatment (20–60 mg/day) due to nausea or orthostatic hypotension.

Table 2 Dose requirements and efficacy of treatment in the 49 patients who received apomorphine therapy for>2 months

	Continuous infusion (n=25)	*Intermittent injection (n=24)*
Infusion rate (mg/h)	4.0 (2.0–6.5)	
Number of injections/day		5.1 (2.0–13)
Bolus dose size of apomorphine (mg)	1.6 (0.5–4.0)	1.9 (0.5–4.5)
Total daily dose of apomorphine (mg)	112.5 (57–174)	9.7 (2–26)
Number of levodopa doses/day before apomorphine	8.0 (4–20)	7.0 (4–15)
Number of levodopa doses/day with apomorphine	7.0 (0–15)	10.0 (5–15)
Total daily dose of levodopa before apomorphine (mg)	900 (400–2600)	825 (175–3000)
Total daily dose of levodopa with apomorphine (mg)	450 (0–1900)	1050 (200–2050)
Part of day in "off" before apomorphine (%)	50.0 (21–77)	50.0 (25–80)
Part of day in "off" with apomorphine (%)	25.0 (10–50)	29.5 (5–60)
Number of "off" periods before apomorphine	4.0 (1.5–10)	4.0 (1–8)
Number of "off" periods with apomorphine	5.0 (2–20)	5.0 (3–8)

Data represent median (range).

Clinical effects

The daily time in "off" was significantly ($p<0.001$) reduced, from 50.0% before treatment to 25.0% with apomorphine (table 2). The percentage reduction of time in "off" correlates to how large a part of the day the patient spent in "off" before apomorphine ($r_s=0.71$), so that patients with more "off" time improved relatively more (data not shown). The number of "off" periods increased slightly but not significantly from 4.0 before apomorphine treatment, to 5.0 "off" periods a day with apomorphine (table 2).

Seventeen of the infusion patients were evaluated at two different time points (data not shown). The time spent in "off" was significantly ($p<0.001$) reduced from 57.0 (21–74)% to 20.0 (10–45)% at the first evaluation (median value 20.2 months). At the second evaluation (after 54.0 months), the time spent in "off" for these patients was 22.0 (10–50)%. The difference between the two evaluations was not significant ($p>0.05$).

The median Hoehn and Yahr stages improved significantly in both "on" (before apomorphine 3.0; with apomorphine 2.5; $p=0.02$) and "off" (before 4.5; with 4.0; $p<0.001$). The Hoehn and Yahr score in "on" improved in 10, was unchanged in 12, and worsened in three out of the 25 patients. The score in "off" improved in 16, was unchanged in eight, and worsened in one patient.

The Schwab and England scores also indicated an improvement. In "on", the median score before apomorphine was 70% and with the treatment 80% ($p<0.001$) and in "off" the Schwab and England scores changed from 40% before apomorphine to 50% with apomorphine ($p<0.001$). The Schwab and England score in "on" improved in 17 and was unchanged in eight out of the 25 patients. The score in "off" improved in 19, was unchanged in three, and worsened in three patients.

Dyskinesias were estimated according to the Obeso scale. Before the treatment the patients had an intensity score of 2.2 (range 0–4) and a duration score of 1.7 (0–3). With apomorphine treatment the scores remained largely unchanged (1.9 (0–4) for the intensity and 1.5 (0–3) for duration). In seven out of 25 patients the dyskinesia intensity improved, in nine patients it remained unchanged, and in nine patients it became worse. The duration of the dyskinesias decreased in five patients, was unchanged in 12 patients, and increased in eight patients.

Table 3 Side effects

	Continuous infusion (n=25)	*Intermittent injections (n=24)*
Local:		
Nodules	All	—
Abscess	1	—
Necrosis	1	—
Systemic:		
Orthostatic hypotension	4	4
Nausea	1	8
Hyperlibidinous effect	1	—
"Urinary urge"	2	—
Diarrhoea	1	1
Nasal congestion	—	2
Sleep disturbance	—	2
Vertigo	—	2
Headache	—	1
Yawning	—	1
Psychiatric:		
Psychosis	5	—
Visual hallucination	3	2
Illusion	1	—
Confusion	1	1
Nightmare	1	—

In the global impression rating, no patient described overall worsening of the parkinsonism, three felt unchanged, six experienced a slight improvement, and 16 a clear improvement. This was in good agreement with the examiners' impression: no patient worsened, two patients were unchanged (the same patients who described themselves as unchanged), seven slightly improved, and 16 clearly improved.

Side effects

The frequency of reported side effects is given in table 3. Minor local irritations (nodules) were present in all patients with apomorphine infusions but none led to termination of the treatment. One patient developed an abscess, which was successfully treated (surgical debridement and antibiotics), and one patient with diabetes mellitus developed necrotic areas at the infusion sites. Four patients developed orthostatic hypotension, two patients noticed increased urinary urge, and one of them also developed diarrhoea. One patient experienced nausea. A 76 year old male patient became hyperlibidinous. This symptom disappeared after administration of goserelin (gonadotrophin releasing hormone agonist; 3.6 mg subcutaneously each month). Later, goserelin could be stopped during continued apomorphine treatment without recurrence of the symptom.

Psychiatric changes were seen in 11 patients: five became psychotic, three had visual hallucinations, one had intermittent illusions, one was confused, and one had occasional nightmares. When comparing the characteristics of the group developing psychiatric side effects with those who did not (table 4) there were no significant differences for age, duration of disease, and age at disease onset. The effect of the treatment, as measured in daily "off" time was also comparable between the two groups and there were no significant differences in dose requirements over time (table 4). The frequency of cognitive problems was, however, clearly

Table 4 Characteristics of patients developing or not developing psychiatric side effects during apomorphine infusion therapy

	Patients with psychiatric side effects (n=11)	*Patients without psychiatric side effects (n=14)*
Age (y)	66.5 (7.4)	63.0 (6.8)
Duration of disease (y)*	17.8 (11–32)	20.1 (12–20)
Duration of levodopa therapy (y)*	16.1 (10–25)	18.5 (12–25)
Duration of "on-off" fluctuations (y)*	11.9 (7–24)	11.7 (4–16)
Daily medication after 1–2 months of apomorphine treatment:		
Levodopa	425 (0–1150) mg/day	400 (0–1150) mg/day
Apomorphine	80.0 (60–151) mg/day	96.5 (62–190) mg/day
Daily medication after a mean of 40.3 (9–66) months of apomorphine treatment:		
Levodopa	400 (0–1250) mg/day	325 (0–1950) mg/day
Apomorphine	105.0 (63–161) mg/day	118 (57–174) mg/day
Part of day in "off" before apomorphine (%)	54.7 (32–77)	49.5 (21–74)
Part of day in "off" with apomorphine (%)	26.8 (10–50)	26.4 (10–50)
Number of patients having cognitive difficulties (%):		
At inclusion in study†	4 (36%)	1 (7%)
At final evaluation†	7 (64%)	2 (14%)

Except for "age" (where mean (SD) are shown) data represent median (range).
*At final evaluation.
†As estimated from clinical examination and assessment during the 5 day pretreatment evaluation period and follow up visits (see methods).

higher in the group developing psychiatric side effects. Four out of 11 patients had cognitive problems when starting apomorphine and seven out of 11 at the final evaluation, compared with one and two, respectively, out of the 14 patients who did not develop psychiatric side effects. Hallucinations and psychotic symptoms could, at least temporarily, be treated by lowering the antiparkinsonian medication or adding clozapine (3.25–50 mg/day).

APOMORPHINE INJECTIONS

Patient group

We followed up 24 patients (16 men, eight women) treated with subcutaneous injections of apomorphine for more than 2 months (median value 22.0 months). Further patient characteristics are given in table 1. In total 15 of the patients stopped the treatment during the study: five showed insufficient effect, three had technical difficulties handling the injections, three developed nausea, two psychiatric side effects, one orthostatism, and one entered another study.

Apomorphine and levodopa doses

The lowest effective dose in the apomorphine dose test was 2.0 (0.5–5.0) mg, the time to onset 10.0 (3–30) minutes, and the duration of the drug effect 47.5 (25–90) minutes. The patients used 5.1 injections a day with a single dose of 1.9 mg, which led to a total daily injection dose of 9.7 mg. Ten patients did not change the antiparkinsonian medication, six patients decreased the levodopa doses, and 12 patients had to increase their medication over the follow up period. The total levodopa dose did, however, not change significantly (825 mg at inclusion and 1050 mg at the final evaluation). The number of levodopa doses a day increased slightly ($p=0.027$), from 7.0 to 10.0. Domperidone could be stopped in all cases except for six patients who still received the treatment (20–60 mg/day) due to nausea or orthostatic hypotension.

Clinical effects

The time spent in "off" was significantly ($p<0.001$) reduced from 50.0% before treatment to 29.5% with apomorphine (table 2). The number of "off" periods a day significantly ($p<0.001$) increased from 4.0 to 5.0.

Ten patients were evaluated on two occasions after a mean of 10.2 and 42.2 months, respectively. The initial time spent in "off" before apomorphine treatment in this group was 50.0% (25–70%). At the first evaluation it reduced significantly ($p=0.012$) to 26.5 (14–45)%. At the second evaluation this had not changed significantly (29.0 (10–50)%)

The Hoehn and Yahr staging in "on" and "off" did not show any significant changes with the apomorphine treatment ("on" without apomorphine 2.5, with 2.5; "off" without: 4.0, with 3.5). The Hoehn and Yahr score in "on" improved in four, was unchanged in 19, and deteriorated in one out of the 24 patients. The score in "off" improved in seven, was unchanged in 14, and worsened in three patients.

For the Schwab and England score there was a significant ($p=0.027$) improvement in "off", but not in "on" ("on" without and with 90%; "off" without 60%, with apomorphine 70%). The Schwab and England score in "on" improved in three, was unchanged in 19, and became worse in two out of the 24 patients. The score in "off" improved in seven, was unchanged in 16, and worsened in one patient.

The dyskinesia intensity score in "on" without and with apomorphine was relatively unchanged (1.7 (0–4)) and 1.6 (0–4) respectively) and the duration score without was 1.3 (0–3) and with apomorphine 1.4 (0–3). In two out of 24 patients the dyskinesia intensity improved, in 19 patients it remained unchanged, and in three patients it became worse. The duration of the dyskinesias decreased in two patients, became unchanged in 19 patients, and increased in three patients.

In the global impression ratings 10 patients stated clear improvement, eight slight improvement, five did not feel any change, one thought it was somewhat worse, but no patient reported much worsening. The same evaluation done by the examiner gave similar results, with clear improvement in 11 patients, slight improvement in nine, and four showed no change. None of the patients were rated worse.

Side effects

No major local reactions at the injection sites were seen in the injection group (table 3). The most frequent side effect was nausea (eight patients) which had to be treated with long term domperidone in three patients. Four patients developed orthostatic hypotension, two nasal congestion, two sleep disturbances, two vertigo, and one diarrhoea. One patient reported headache and one yawning. Psychiatric side effects were rare. Two patients experienced visual hallucinations and one patient was confused after some of the injections.

Discussion

We followed up 25 patients treated with subcutaneous continuous apomorphine infusions and 24 patients treated with intermittent apomorphine injections for more than two

months, and up to 5.5 years. The patients in both groups showed good compliance. The most prominent effect was a significant reduction of the daily time spent in "off" from 50 to 25% in the infusion group and from 50 to 30% in the injection group, which is well compatible with the findings reported by other authors.[13] With the continuous infusion therapy there was often also an improvement of the quality of the "on " and "off" phases, as demonstrated with the Hoehn and Yahr and the Schwab and England scales. The fact that the daily number of "off" periods slightly increased over time with apomorphine can probably be explained by a fragmentation of otherwise longer "off" periods. The effect on peak dose and biphasic dyskinesias was, as also reported by other authors,[48] less pronounced. Our experience, however, is that individual patients may also benefit significantly from apomorphine in this respect. Furthermore, painful dystonias did in some cases respond very well to apomorphine. This study does not indicate any development of tolerance to infused apomorphine as the doses and the effects were relatively stable over the observation period.

The design of the study does not include randomisation of the patients to the different treatment groups. The reason for this was that our primary goal was to support each of the patients with the most optimal form of therapy. It was, from our own as well as other's experience, obvious that apomorphine injections and infusions are suitable for different groups of patients. In most cases it was evident which treatment would be best in the individual case and it was thus difficult to rectify a random allocation of the patients to these treatment groups. This makes it difficult to draw conclusions of the relative effect of the different applications of apomorphine treatment. Statistically, there was, however, no confounding effect from the composition of the treated groups for age, duration of disease, duration of levodopa treatment or duration of "on-off" symptomatology, regarding the outcome in terms of time in "off".

The fact that there is not a control group with peroral treatment also limits the possibility of comparing apomorphine with traditional peroral treatment as the patients' disease is progressing during the course of the treatment. Comparison is thus only possible with the patients themselves before and after apomorphine treatment. However, the effect of this should probably be an underestimation rather than an overestimation of the positive effects of the treatment. Controlled studies with randomisation, comparing the effect of peroral treatment, apomorphine injections, apomorphine infusions, and maybe also other novel pharmacological as well as neurosurgical interventions, would be of high clinical relevance, but would require large multicentre study designs. A placebo control was not included in the present study as the antiparkinsonian effect of apomorphine is very well established and was part of an earlier apomorphine study in which we participated.[19]

All patients who received infusions developed minor local skin reactions but none of these forced the treatment to be stopped. The severity of these local reactions seemed to be related to the total daily dose of apomorphine. In one patient the infusion site nodule became infected and required incision, drainage, and treatment with antibiotics. After the experiences from our first 10 patients receiving apomorphine infusion, we increased the frequency of changes of infusion sites from once to twice a day and saw a clearly lower frequency and severity of the local side effects. According to the experience from other groups there is less skin reaction when using 5 instead of 10 mg/ml apomorphine. We only have experience of using a 5 mg/ml solution. In patients with pronounced reactions we applied mucopolysaccharide locally three times daily. The effect of this was not studied in a controlled way, but the clinical impression was that this was beneficial. We did not try mucopolysaccharide prophylactically, which might be of interest. From other centres it has been suggested that ultrasonic treatment of the nodules will accelerate their disappearance.[13] Injections of 5 mg/ml apomorphine did, by contrast with the infusions, never cause formation of nodules. At most the patients felt a slight irritation at the injection place.

In the patients with infusion therapy, psychiatric symptoms were the most severe side effects. Eleven (44%) of the infusion patients, but only three (12%) of the patients using pen injections developed psychiatric side effects. One explanation for this difference could be the higher total daily dose of apomorphine in the infusion patients compared with the pen patients (table 2). It can also be speculated that patient characteristics may be a contributing factor for the higher frequency of psychiatric side effects in the infusion group. These patients had significantly more severe Hoehn and Yahr stages than the injection group ($p=0.001$) and longer duration of disease ($p=0.002$) as well as levodopa therapy ($p=0.004$, table 1).

No significant differences in patient characteristics, dose requirements, or efficacy of treatment were found between infusion patients who did and did not develop psyciatric side effects. However, there seems to be a clear association between cognitive decline and development of psychotic symptoms (table 4). Thirty six per cent and 64% of those patients who developed psychiatric side effects exhibited clinical signs of cognitive difficulties at inclusion in the study and at the final evaluation, respectively. These proportions could have been even higher if the intellectual function had been formally tested—for example, with the mini mental status examination. This implies that cognitive decline should be regarded as a relative contraindication for treatment with continuous infusion of apomorphine.

In most cases a reduction of the antiparkinsonian treatment and in some cases the addition of closapine could eliminate or at least reduce the psychiatric symptoms to an acceptable level. By these means most patients could

continue the apomorphine treatment, whereas five (10%) of the patients had to stop the treatment due to psychiatric side effects. These patients were later treated with peroral drugs resulting in less intense psychiatric problems but also in a worsened motor condition. One patient who developed paranoid psychiatric symptoms on apomorphine infusion was later transferred to treatment with continuous intraduodenal levodopa infusion. This treatment gave comparable effects and has so far (after 18 months) not produced any psychiatric side effects. It may be pointed out, however, that the levodopa infusion is given during 16 hours each day, whereas apomorphine was given 24 hours a day. It is still not completely clear if apomorphine has more, equal, or less tendency to produce psychiatric side effects compared with other dopaminergic drugs.[22 29] The relatively high frequency of psychiatric side effects seen in this study could be the result of optimising the antiparkinsonian treatment in this severely ill and rather old group of patients.

The patients with pen injections showed a relatively high incidence of nausea (eight patients (33%)) compared with infusion patients (one patient (5%)). This is probably due to a down regulation of the medullary dopamine receptor sensitivity secondary to continuous dopaminergic stimulation, leading to a lower frequency of nausea in the infusion group. This view is strengthened by the fact that nausea in the injection group mainly occurred in patients who injected themselves with low frequency (<4 times a day).

Orthostatic hypotension became symptomatic in four patients (16%) on infusions and four patients (17%) on injections. Domperidone was also helpful in counteracting this side effect except for one patient, who stopped the treatment because of orthostatic hypotension.

One of the infusion patients developed haemolytic anaemia which was reversed after discontinuation of apomorphine. Single cases of this complication have been reported earlier.[13]

A total of 20 patients treated for more than 3 months stopped the apomorphine treatment. This included several patients who initially showed a good therapeutic effect and reflects a necessity to continuously re-evaluate the effect of the treatment in relation to side effects. Apomorphine should thus not necessarily be seen as a lifelong treatment, but rather as an adjuvant therapy during some years of the advanced disease. Particularly when cognitive deficits add to the motor symptoms, the benefit of this treatment often becomes less apparent and the problems handling the apparatus increase.

The present study confirms that apomorphine treatment in Parkinson's disease significantly reduces the time spent in "off". In the group of patients who received continuous infusion of apomorphine, the time spent in "off" decreased from 57 to 20% at the first evaluation compared with before the treatment. At the second evaluation this effect was stable (22% of the day in "off"). Other authors have stated that treatment with continuous dopaminergic stimulation might have a stabilising influence on "on-off" fluctuations not only initially, but also over prolonged periods.[12] Our experience confirms these results. One possible explanation would be that continuous dopaminergic stimulation is closer to the physiological situation and could be favourable for postsynaptic receptor mechanisms involved in the development of motor fluctuations during intermittent dopaminergic stimulation.[49] A second possibility would be a neuroprotective effect of the treatment, slowing down the progression of the illness. This hypothesis would be supported by the finding that apomorphine can act as a free radical scavenger with capacity to limit the oxidative stress which has been suggested to be of importance for the neurodegeneration in Parkinson's disease.[50 51] A third explanation could be that the severely ill patients who have received continuous infusion treatment might have reached a plateau in their illness with less rapid progression of the symptomatology or complications of therapy. If it can be firmly demonstrated that continuous dopaminergic stimulation halts the progression of symptomatology, the indications for such a type of therapy could be considerably broadened. It should then also be used earlier in the disease. Specially designed long term studies will be needed to consider these questions.

For a successful outcome of this therapy, careful selection and follow up of patients seems to be paramount. Our impression is that injections of apomorphine can be attempted in most patients who, despite optimised peroral treatment, have recurring "off" periods. The best results, however, are obtained with relatively young, cognitively intact, active, and well motivated patients. In this group the treatment often significantly improves the possibility to continue work and live a normal social life.

Continuous infusion of apomorphine should be tried in patients who, despite optimised peroral treatment and injection treatment with apomorphine, show incapacitating motor fluctuations. The best effect is seen if the patient is cognitively well preserved, well motivated, and has not previously shown psychiatric side effects on dopaminergic treatment. It should be avoided in patients with cognitive impairment and patients who have shown a tendency to develop psychiatric side effects on other antiparkinsonian agents. It is our opinion that injection and infusion treatment with dopaminergic drugs in general should be tried before more irreversible neurosurgical methods. A combination of apomorphine with surgical methods such as pallidal stimulation constitute tempting novel therapeutic approaches. With respect to the seemingly clear antidyskinetic and often less pronounced antiakinetic effect of pallidum surgery[52] such a combined approach may have the potency to offer valuable improvements for the severely disabled, cognitively intact patient with Parkinson's disease.

We conclude that even after an extended period of apomorphine treatment of more than 5 years it is still possible to treat disabling symptoms of Parkinson's disease. With a care-

ful patient selection and thorough follow up, injection and infusion of apomorphine is an effective and reliable treatment which can improve the motor status and quality of life in parkinsonian patients. This modality of treatment warrants wider application.

This study was supported by the Swedish Medical Research Council and the Medical Faculty of the University of Lund. KP was supported by a grant from the Deutsche Forschungsgemeinschaft (PI 268/1–1). We thank the patients for their cooperation, Professor Olle Lindvall for excellent collaboration and support, and Mrs Maria Török for expert statistical assistance, Lene Mangalanayagam and Christine Nilsson for expert nursing assistance and data collection, Jan Reimer, Lena Quittberg, and Anne F Wieberg for expert nurse assistance, Elisabeth Rasmusson for secreterial work, and the Department of Neurology at the University Hospital in Lund, Sweden, for facilities.

1 Quinn N. Drug treatment of Parkinson's disease. *BMJ* 1995;**310**:575–9.
2 Nutt JG, Woodward WR, Hammerstad JP, *et al*. The on-off phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984;**310**:483–8.
3 Schwab RS, Amador LV, Levine JY. Apomorphine in Parkinson's disease. *Trans Am Neurol Assoc* 1951;**76**:251–3.
4 Neumeyer JL, Samarthji L, Baldessarini RJ. Historical highlights of the chemistry, pharmacology and early clinical uses of apomorphine. In: Gesse GL, Corsini GU, eds. *Apomorphine and other dopaminomimetics. Pharmacology.* New York: Raven Press, 1981.
5 Gancher ST, Woodward WR, Boucher B, *et al*. Peripheral pharmacokinetics of apomorphine in humans. *Ann Neurol* 1989;**26**:232–8.
6 Gancher S. Pharmacokinetics of apomorphine in Parkinson's disease. *J Neural Transm Suppl* 1995;**45**:137–41.
7 Neef C, Jelliffe RW, Laar TV, *et al*. Population pharmacokinetics of apomorphine in patients with Parkinson's disease. *Drug Invest* 1994;**7**:183–90.
8 Nicolle E, Pollak P, Serre-Debeauvais F, *et al*. Pharmacokinetics of apomorphine in parkinsonian patients. *Fundam Clin Pharmacol* 1993;**7**:245–52.
9 Przedborski S, Levivier M, Raftopoulos C, *et al*. Peripheral and central pharmacokinetics of apomorphine and its effects on dopamine metabolism in humans. *Mov Disord* 1995;**10**:28–36.
10 Corsini GU, Del Zompo M, Gessa GL, *et al*. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. *Lancet* 1979;i:954–6.
11 Frankel JP, Lees AJ, Kempster PA, *et al*. Subcutaneous apomorphine in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:96–101.
12 Gancher ST, Nutt JG, Woodward WR. Apomorphine infusional therapy in Parkinson's disease: clinical utility and lack of tolerance. *Mov Disord* 1995;**10**:37–43.
13 Hughes AJ, Bishop S, Kleedorfer B, *et al*. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. *Mov Disord* 1993;**8**:165–70.
14 Kreczy-Kleedorfer B, Wagner M, Bösch S, *et al*. Langzeitergebnisse kontinuerlicher subkutaner Apomorphinpumpentherapie bei Patienten mit fortgeschrittener Parkinson-Krankheit. *Nervenarzt* 1993;**64**:221–5.
15 Lees AJ. Dopamine agonists in Parkinson's disease: a look at apomorphine. *Fundam Clin Pharmacol* 1993;**7**:121–8.
16 Muguet D, Broussolle E, Chazot G. Apomorphine in patients with Parkinson's disease. *Biomed Pharmacother* 1995;**49**:197–209.
17 Pollak P, Champay AS, Hommel M, *et al*. Subcutaneous apomorphine in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989;**52**:544.
18 Stibe CMH, Kempster PA, Lees AJ, *et al*. Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988;i:403–6.
19 Östergaard L, Werdelin L, Odin P, *et al*. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995;**58**:681–7.
20 Chaudhuri KR, Critchley P, Abbott RJ, *et al*. Subcutaneous apomorphine for on-off oscillations in Parkinson's disease. *Lancet* 1988;ii:1260.
21 Colosimo C, Merello M, Albanese A. Clinical usefulness of apomorphine in movement disorders. *Clin Neuropharmacol* 1994;**17**:243–59.
22 Ellis C, Lemmens G, Parkes JD, *et al*. Use of apomorphine in Parkinsonian patients with neuropsychiatric complications to oral treatment. *Parkinsonism and Related Disorders* 1997;**3**:103–7.
23 Galvez-Jimenez N, Lang AE. Perioperative problems in Parkinson's disease and their management: apomorphine with rectal domperidone. *Can J Neurol Sci* 1996;**23**:198–203.
24 Kempster PA, Frankel JP, Stern GM, *et al*. Comparison of motor response to apomorphine and levodopa in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:1004–7.
25 Kempster PA, Iansek R, Larmour I. Intermittent subcutaneous apomorphine injection treatment for Parkinsonian motor oscillations. *Aust NZ J Med* 1991;**21**:314–8.
26 Muhiddin KA, Roche MT, Pearce VR. Subcutaneous apomorphine infusion in Parkinson's disease: does it have a role? *Postgrad Med J* 1994;**70**:344–6.
27 Obeso JA, Grandas F, Vaamonde J, *et al*. Apomorphine infusion for motor fluctuations in Parkinson's disease. *Lancet* 1987;i:1376–7.
28 Poewe W, Kleedorfer B, Wagner M, *et al*. Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease. Long term follow up in 18 patients. In: Narabayashi H, Nagatsu T, Yanagisawa Y, *et al*, eds. *Parkinson's disease: from basic research to treatment.* New York: Raven Press, 1993:656–9. (Advances in neurology, Vol 60.)
29 Ray-Chaudhuri K, Abbott RJ, Millac PAH. Subcutaneous apomorphine for parkinsonian patients with psychiatric side effects on oral treatment. *J Neurol Neurosurg Psychiatry* 1991;**54**:372–3.
30 Rodriguez M, Lera G, Vaamonde J, *et al*. Motor response to apomorphine and levodopa in asymmetic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1994;**57**:562–6.
31 Steiger MJ, Quinn NP, Marsden CD. The clinical use of apomorphine in Parkinson's disease. *J Neurol* 1992;**239**:389–93.
32 Stibe CMH, Lees AJ, Stern GM. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. *Lancet* 1987;i:871.
33 Stocchi F, Bramante L, Monge A, *et al*. Apomorphine and lisuride infusion. A comparative chronic study. In: Narabayashi H, Nagatsu T, Yanagisawa Y, *et al*, eds. *Parkinson's disease: from basic research to treatment.* New York: Raven Press, 1993:653–5. (Advances in neurology, Vol 60.)
34 Corboy DL, Wagner ML, Sage JI. Apomorphine for motor fluctuations and freezing in Parkinson's disease. *Ann Pharmacother* 1995;**29**:282–8.
35 Pollak P, Benabid AL, Limousin P, *et al*. External and implanted pumps for apomorphine infusion in parkinsonism. *Acta Neurochir Suppl (Wien)* 1993;**58**:48–52.
36 Kapoor R, Turjanski N, Frankel J, *et al*. Intranasal apomorphine: a new treatment in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:1015.
37 Kleedorfer B, Turjanski N, Ryan R, *et al*. Intranasal apomorphine in Parkinson's disease. *Neurology* 1991;**41**:761–2.
38 Dewey RB Jr, Maraganore DM, Ahlskog JE, *et al*. Intranasal apomorphine rescue therapy for parkinsonian off periods. *Clin Neuropharmacol* 1996;**19**:193–201.
39 Deffond D, Durif F, Tournilhac M. Apomorphine in treatment of Parkinson's disease: comparison between subcutaneous and sublingual routes. *J Neurol Neurosurg Psychiatry* 1993;**56**:101–3.
40 Durif F, Deffond D, Tournilhac M. Efficacy of sublingual apomorphine in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:1105.
41 Gancher ST, Nutt JG, Woodward WR. Absorption of apomorphine by various routes in parkinsonism. *Mov Disord* 1991;**6**:212–6.
42 Montastruc JL, Rascol O, Senard JM, *et al*. Sublingual apomorphine: a new pharmacological approach in Parkinson's disease? *J Neural Transm Suppl* 1995;**45**:157–61.
43 Hughes AJ, Bishop S, Lees AJ, *et al*. Rectal apomorphine in Parkinson's disease. *Lancet* 1991;**337**:118.
44 van-Laar T, Jansen EN, Neef C, *et al*. Pharmacokinetics and clinical efficacy of rectal apomorphine in patients with Parkinson's disease: a study of five different suppositories. *Mov Disord* 1995;**10**:433–9.
45 Langston JW, Widner H, Goetz CG, *et al*. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;**7**:2–13.
46 Hughes AJ, Lees AJ, Stern GM. Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990;**336**:32–4.
47 Oertel WH, Gasser T, Ippisch R, *et al*. Apomorphine test for dopaminergic responsiveness. *Lancet* 1989;i:1262–3.
48 Durif F, Deffond D, Dordain G, *et al*. Apomorphine and diphasic dyskinesia. *Clin Neuropharmacol* 1994;**17**:99–102.
49 Chase TN, Engber TM, Mouradian MM. Contribution of dopaminergic and glutamatergic mechanisms to the pathogenesis of motor response complications in Parkinson's disease. *Adv Neurol* 1996;**69**:497–501.
50 Gassen M, Glinka Y, Pinchasi B, *et al*. Apomorphine is a highly potent free radical scavenger in rat brain mitochondrial fraction. *Eur J Pharmacol* 1996;**308**:219–25.
51 Gassen M, Glinka Y, Pinchasi B, *et al*. Free radical scavenging activity of the dopamine D1-D2 receptor agonist apomorphine. *Mov Disord* 1996;**11**(suppl 1):195.
52 Johansson F, Malm J, Nordh E, *et al*. Usefulness of pallidotomy in advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;**62**:125–32.